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Can immature granulocyte predict the prognosis of bladder cancer?

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ABSTRACT

Objectives: To determine the diagnostic value of immature granulocyte (IG) count before treatment in patients with invasive bladder cancer and to compare this marker with other routine inflammation markers. *Methods:* In this retrospective observational study, the data of patients who underwent transurethral resection for the diagnosis of bladder cancer were analyzed. Two groups were formed as those with non-muscle invasive bladder cancer (NMIBC) and those with muscle invasive bladder cancer (MIBC). Demographic data, routine laboratory tests, neutrophil/lymphocyte ratio (NLR), red blood cell distribution width (RDW), and IG levels of the groups were recorded and compared. *Results*: There were 57 patients in the NMIBC group and 55 patients in the MIBC group. NLR, RDW and PLR levels were significantly higher in the MIBC group ($p<0.001$, each). In univariate analysis neutrophil, lymphocyte, NLR, IG, and RDW were identified as predictors for MIBC. In multivariate analysis, NLR, RDW and IG were significantly associated with the predictors of MIBC ($p<0.001$,each). Cut-off values were 3.06 for NLR, 11.15 for RDW, and 0.08 for IG. *Conclusion*: IG is an important inflammatory marker included in complete blood count parameters and may be useful in predicting muscle invasion in patients with bladder cancer.

Keywords: Bladder cancer, Immature granulocyte, Neutrophil-lymphocyte ratio, Red blood cell distribution width

1. INTRODUCTION

Bladder cancer is seen as an international public health problem due to environmental factors and smoking. It ranks 10th among all cancers in the world and is the 13th most common cancer cause with nearly 200,000 deaths in 2018. At the time of diagnosis, 70% of bladder cancers are in the non-muscle-invasive stage, while 30% are in the muscle-invasive or metastatic stage (Bray et al., 2018). The diagnosis of muscle invasive cancer is made by transurethral resection of the bladder tumor (TURBT), and the recommended treatment for tumors staged as T2-T4a N0-Nx M0 by clinical evaluation is radical cystectomy (Witjes et al., 2019). Therefore, determination of local tumor depth, lymph node involvement and presence of distant metastasis are important (Spiess et al., 2017).

Recent data suggest that the systemic inflammatory response may play an important role in the development and progression of cancer. Proliferation, invasion and metastasis of malignant cells in tumor cases cause the development of an immune reaction in the organism (Huang et al., 2019). Indicators of the tumor-associated systemic immune response are mostly neutrophilia, relative lymphopenia or thrombocytosis. In addition, increased neutrophil / lymphocyte ratio (NLR) has been shown as a poor prognosis factor in malignancies (Kaynar et al., 2014).

Another inflammatory marker whose relationship with malignancy has been investigated recently is red blood cell distribution width (RDW). RDW shows the distribution width of the sizes of erythrocytes and is traditionally used to evaluate hematological diseases, especially anemia (Parizadeh et al., 2019). However, many studies have shown a close association between RDW and systemic inflammation and reflects the inflammation state associated with cancer (Hsueh et al., 2019). Immature granulocyte (IG) is a new marker of inflammation that is not well known to most clinicians. IG is an indicator of increased myeloid cell production in conditions such as bone marrow activation and infection.Since it was started to be measured with automatic devices, it can be studied simultaneously and quickly with complete blood count (Park et al., 2017). IG values measured in emergencies such as acute pyelonephritis and acute appendicitis have been found useful, but their association with cancer has been shown in a limited number of studies (Barut et al., 2020; Kim et al., 2016).

In our literature review, we could not find any studies on the clinical utility of IG in bladder cancer pathologies. Therefore, we hypothesized that an elevated IG count would be associated with bladder cancer prognosis. In this study, we aimed to determine the diagnostic value of pre-treatment IG count in patients with bladder cancer and to compare it with other routine inflammatory markers such as NLR and RDW.

2. MATERIALS AND METHODS

Study Design and Patients

This retrospective observational study was approved by the Ethics Committee of Kahramanmaras Sutcu Imam University Medical Faculty with number of 2021/07/01. The data of patients who underwent TURBT for bladder cancer diagnosis were analyzed in the period between April 2017 and December 2020 in our clinic. As a result of pathological evaluations, 57 patients with non-muscle invasive bladder cancer (NMIBC, stage pTa or pT1) and 55 patients with muscle invasive bladder cancer (MIBC, stage pT2+) were included in the study and two groups were formed. Patients with other organ malignancies, hematological disease, using anticoagulant drugs, who had blood transfusion in the last two months, and who had undisclosed leukocytosis and active infection were excluded from the study.

Data collection

Demographic data such as age and gender, preoperative routine laboratory tests, tumor size and tumor number of both groups were recorded. A specific automated cell analyzer (XN 3000; Sysmex Corp., Kobe, Japan) was used to determine the IG count (10^9/L), RDW (%) and other hematological parameters. The NLR was calculated manually by dividing the neutrophil count by the number of lymphocytes.

The surgical specimens were evaluated by genitourinary pathologists. Tumor staging was performed according to the 2009 tumor node metastasis (TNM) classification (7th edition). Tumor grade was determined according to the 2004 World Health Organization system.

Statistical Analysis

SPSS 22 (SPSS, Inc. Chicago, IL) program was used for data analysis. Continuous variables were expressed as means and standard deviations (SD) or medians and interquartile ranges (IQR). The independent t-test or Mann–Whitney U test was utilized for continuous variables. Chi-square test or Fisher's exact test was used for categorical variables. The independent factors associated with MIBC were evaluated using univariate and multivariate analysis. Receiver operating characteristic (ROC) curve analysis was used to determine the cut-off values of NLR, RDW and IG levels for MIBC patients, and area under the curve (AUC), sensitivity and specificity values were calculated. A p-value <0.05 was considered statistically significant.

3. RESULTS

The mean age of 57 (50.9%) patients in the NMIBC group was 67.12 ± 12.42 and the mean age of 55 (49.1%) patients in the MIBC group was 65.74 ± 11.14 (P = 0.538). The male to female ratio was 4.7: 1 in the NMIBC group and 4: 1 in the MIBC group, and no significant difference was observed (P = 0.739). In the MIBC group, the neutrophil count was significantly higher and the

lymphocyte count was lower (P<0.001, each). The levels of inflammatory markers NLR, IG and RDW were significantly higher in the MIBC group (4.25 vs. 2.21, 0.210⁹/L vs. 0.04 10⁹/L, and 13.50 % vs. 8.70 %, respectively and P < 0.001, each). There was no significant difference between the groups in terms of tumor size and tumor number. The percentage of high grade tumors was statistically higher in the MIBC group (P < 0.001). The demographic characteristics and pathology results of the groups are shown in Table 1 in detail.

Table 1 Demographic and clinical data of patients with bladder cancer

Variables	NMIBC (pTa/T1) group	MIBC(pT2+) group	p
Patients, n (%)	57 (50.9)	55 (49.1)	
Age (years)	67.12 ± 12.42	65.74 ± 11.14	0.538
Gender, n (%)			0.739
Male	47 (82.5)	44 (80.0)	
Female	10 (17.5)	11 (20.0)	
Tumour size (cm), n (%)			0.348
< 3 (small)	18 (31.6)	13 (23.6)	
≥ 3 (large)	39 (68.4)	42 (76.4)	
Tumour number			0.125
Solitary	42 (73.7)	43 (78.2)	
Multiple	15 (26.3)	12 (21.8)	
Tumour grade, n (%)			0.001
Low (G1/G2)	41 (71.9)	22 (40.0)	
High (G3)	16 (28.1)	33 (60.0)	
Median laboratory tests (range)			
WBC (10⁹/L)	8.34 (7.11 – 10.17)	7.86 (6.29 – 11.22)	0.880
Neutrophil (10⁹/L)	5.12 (4.01 – 6.03)	6.72 (4.86 – 8.63)	< 0.001
Lymphocyte (10⁹/L)	2.16 (1.76 – 2.66)	1.45 (1.06 – 2.12)	< 0.001
NLR	2.21 (1.88 – 2.81)	4.25 (3.52 – 6.54)	< 0.001
IG (10⁹/L)	0.04 (0.02 – 0.05)	0.2 (0.09 – 0.40)	< 0.001
RDW (%)	8.70 (7.85 – 9.70)	13.50 (11.60 – 15.40)	< 0.001

NMIBC: Non-muscle invasive bladder cancer; MIBC: Muscle invasive bladder cancer; WBC: White blood cells; NLR: Neutrophil / lymphocyte ratio; IG: Immature granulocyte; RDW: Red blood cell distribution width

In univariate analysis neutrophil (P < 0.001), lymphocyte (P < 0.001), NLR (P = 0.002), IG (P < 0.001), and RDW (P < 0.001) were identified as predictors for MIBC. In multivariate analysis, NLR value (odds ratio (OR) = 0.414, 95% confidence interval (CI) = 4.691-7.416, P < 0.001), IG (OR = 0.534, 95% CI = 0.235-0.337, P < 0.001), and RDW (OR = 0.956, 95% CI = 13.175-14.292, P < 0.001) were significantly associated with the predictors of MIBC (Table 2).

Table 2 Univariate and multivariate analyses for the prediction of MIBC.

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	OR (95% CI)	p
Age	0.003 (-3.051-5.805)	0.539		
WBC	0.008 (-1.876-0.686)	0.359		
Neutrophil	0.130 (-3.063-1.054)	<0.001		
Lymphocyte	0.129 (0.319-0.934)	<0.001		
NLR	0.085 (-4.990-1.171)	0.002	0.414 (4.691-7.416)	<0.001
IG	0.293 (-0.312-0.170)	<0.001	0.534 (0.235-0.337)	<0.001
RDW	0.582 (-5.669-4.103)	<0.001	0.956 (13.175-14.292)	<0.001

OR:Odds ratio; CI: Confidence interval; NLR: Neutrophil / lymphocyte ratio; IG: Immature granulocyte; RDW: Red blood cell distribution width

We performed ROC analysis to determine the sensitivity, specificity and recommended cut-off values of NLR, IG and RDW as predictor factors in MIBC. The cut-off value for NLR was 3.06 with 81.8% sensitivity and 82.5% specificity (AUC = 0.854 95% CI = 0.782-0.925, P < 0.001), the cut-off value for IG was 0.08 with 83.6% sensitivity and 84.2% specificity (AUC = 0.910, 95% CI = 0.858-0.962, P < 0.001) and the cut-off value for RDW was 11.15 with 85.5% sensitivity and 87.7% specificity (AUC = 0.963, 95% CI = 0.929-0.997, P < 0.001) (Table 3). Figure 1 shows the ROC curves.

Table 3 ROC curves of inflammatory markersfor MIBC patients.

Variables	AUC (95% CI)	Cut-off	Sensitivity (%)	Specificity (%)	p
NLR	0.854 (0.782-0.925)	3.06	81.8	82.5	< 0.001
IG	0.910 (0.858-0.962)	0.08	83.6	84.2	< 0.001
RDW	0.963 (0.929-0.997)	11.15	85.5	87.7	< 0.001

AUC: Area under the curve; CI: Confidence interval; NLR: Neutrophil / lymphocyte ratio; IG: Immature granulocyte; RDW: Red blood cell distribution width

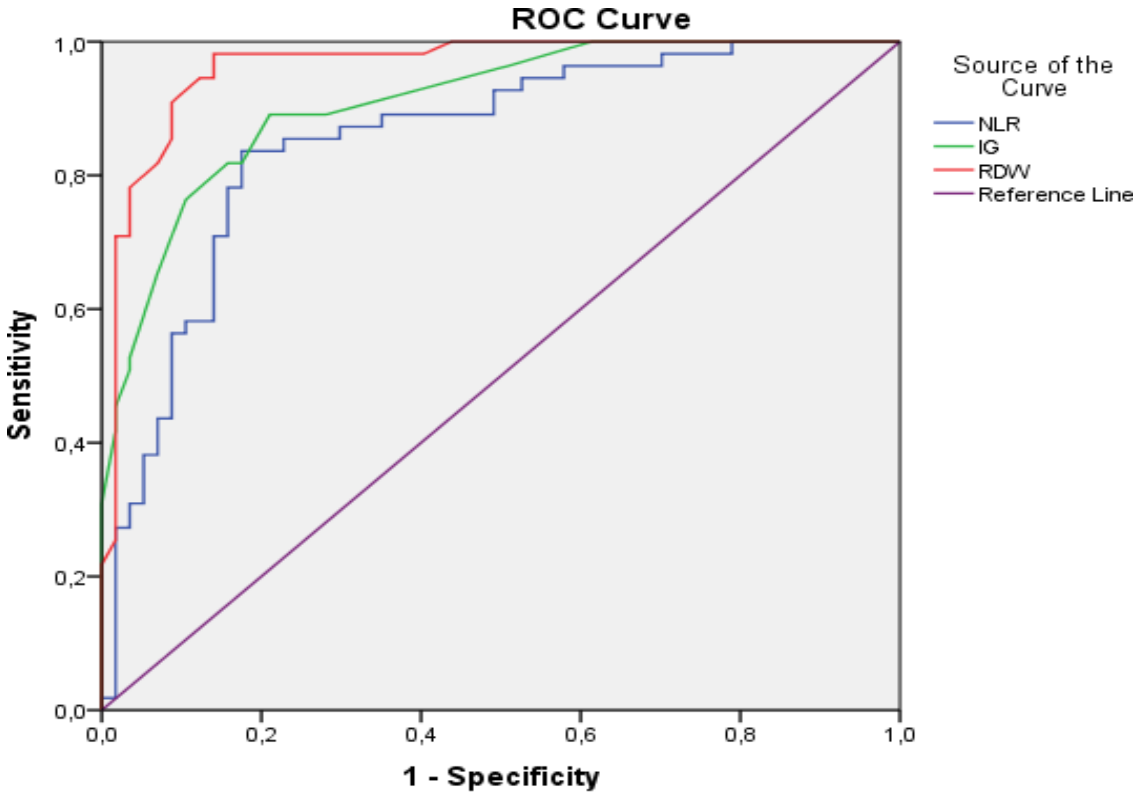

Figure 1 ROC curves of NLR, IG, and RDW for MIBC patients

4. DISCUSSION

It is known that systemic inflammation plays an important role in cancer progression and metastasis development in many types of cancer, including bladder cancer (Huang et al., 2019). Although there are many studies on NLR and RDW in bladder cancer cases, there are no studies on IG. We investigated the predictive effect of IG in peripheral blood in bladder cancer and we found that serum IG level was higher in pre-treatment MIBC patients compared to NIMBC patients. This study shows that the increase in serum IG level, which can be operated with automated systems and is among the parameters of complete blood count, may be a useful infection marker in the prediction of invasive bladder cancer.

Studies have revealed that systemic inflammatory markers are associated with the prediction and prognosis of invasive bladder cancer. NLR, one of these markers, has a wide range of uses and is also a low cost and easily accessible parameter (Çelen et al., 2019). An increase in NLR is characterized by an increase in serum neutrophil levels and / or a decrease in lymphocyte count. Schepisi et al. (2016) described the relationship between NLR and cytokines in tumor pathophysiology. The authors demonstrated that the high circulating neutrophil level was associated with the increase of cytokines, in particular interleukins (IL-1, IL-6), and

pro-angiogenic vascular endothelial growth factor that promotes tumor migration and proliferation. The prognostic role of NLR was first described in many non-urological malignancies such as gastric, hepatic, non-small cell and cervical cancer (Gomez et al., 2008; Jung et al., 2011; Tomita et al., 2011).

In recent years, new studies have similarly revealed the importance of NLR in urological malignancies (Jang et al., 2016). Viers et al. (2014) showed that preoperative NLR was associated with greater lymph node invasion, higher recurrence rates, and poorer cancer-specific survival in patients undergoing radical cystectomy for urothelial bladder cancer. Rossi et al. (2015) determined that progression-free survival was 3.2 months in patients with NLR ≥ 3.0 and 6.9 in patients with < 3.0. In addition, when they evaluated the patients before and after chemotherapy, they found that the NLR level was higher in the bad prognosis group. Gondo et al. (2012) reported that NLR cut-off value ≥ 2.5 in bladder cancer patients was an independent strong prognostic factor for disease-specific survival risk.

In another study, Aydın et al. (2019) showed that high NLR value in non-muscle invasive bladder cancer patients was associated with T1 tumor, high grade, multiple tumors, >3cm tumor and EORTC high risk group.In our study, we found that NLR was significantly higher in the MIBC group compared to the NMBIC group. We calculated a cut-off value of 3.06 for NLR at sensitivity and specificity of 81.8% and 82.5%, respectively, using the ROC curve. RDW elevation is known as the increase in the heterogeneity of reticulocytes in peripheral blood and has been shown to reflect the inflammatory state of the body.

Recently, there are various studies regarding the use of RDW in the diagnosis and follow-up of malignant tumors and high RDW has been reported to be associated with poor prognosis (Hu et al., 2017). Cheng et al. (2016) reported that high RDW value was associated with poor prognosis in patients with upper urinary tract urothelial carcinoma. Ma et al. (2020) showed that high RDW value was a risk factor for poor prognosis after radical cystectomy in patients with bladder cancer. Luo et al. (2018) found a significant difference in pretreatment RDW value between patients with bladder cancer and the control group.

In a study of 152 patients with urothelial carcinoma who underwent radical cystectomy due to MIBC, high RDW was found to be a good prognostic parameter for progression-free survival and overall survival (Yılmaz et al., 2020). In the present study, we showed that RDW was higher in the MBIC group, furthermore, RDW was identified as an independent prognostic factor in multivariate analysis. IG is a new inflammatory marker that is automatically measured in new generation automated devices. It has been shown in recent studies to provide information about the early diagnosis and prognosis of sepsis (Park et al., 2011). Seok et al. (2012) compared the IG percentages in the systemic inflammatory response syndrome, sepsis, and severe sepsis groups and reported that this value was significantly higher in the severe sepsis group. There are studies showing that IG value and percentage increase in emergency situations such as acute appendicitis, acute cholecystitis and acute pyelonephritis. These studies showed that IG value and percentage were more valuable parameters than other inflammatory markers (Kim et al., 2016; Lee et al., 2019; Barut et al., 2020).

We did not find any study evaluating the relationship between IG count and bladder cancer in the literature. There are a limited number of studies on other malignancies. Bozan et al. (2020) compared the preoperative IG levels in patients with nodular goiter and thyroid malignancies. They showed that the IG level was significantly higher in the group of patients with thyroid malignancies at 83% sensitivity and 72.1% specificity. In another study, Barut et al. (2021) found that the percentage of IG was significantly higher in patients with kidney cancer than in the control group. The authors reported that the IG percentage was a very important marker in predicting kidney cancer, with a sensitivity of 82.2% and a specificity of 83.1%.

In our study, the IG count was significantly higher in the MIBC group (P <0.001). In addition, we concluded that IG was a very useful inflammatory marker with 83.6% sensitivity and 84.2% specificity at 0.08 10^9 / L cut-off value in predicting MIBC. Our univariate and multivariate analyzes showed that IG, like other inflammatory markers such as NLR and RDW, was an important predictor of MIBC. Our findings suggest that IG count may be a promising marker for invasive bladder cancer and may be included in predictive nomograms in the future.

The main limitations of our study were its single center and retrospective design. Therefore, the number of patients included in the study was low. In addition, the short follow-up period of the patients was another limitation. However, the major advantage of our study is its ability to demonstrate the usability of IG, an easily accessible and inexpensive test for predicting MIBC. Larger, prospective studies are needed to fully define the benefit of IG clinically.

5. CONCLUSION

IG is an important inflammatory marker included in the parameters of complete blood count and may be useful in predicting muscle invasion in patients undergoing TURBT for bladder cancer. IG can be a promising marker in the diagnosis and follow-up planning of invasive bladder cancer.

Ethical approval

This study was approved by Kahramanmaras Sutçu Imam University Medical Ethics Committee, (Ref no. 2021/07/01) Turkey.

Informed consent

Written and oral informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this manuscript.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

The authors declare that there are no conflicts of interests.

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Author's contribution

All authors conceptualized, designed, and carried out the study, collected and analyzed data. All authors read and agreed the final manuscript.

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